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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
ANGELL, JON E	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 07/26/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/787,559	KRAMER ET AL.	
	Examiner	Art Unit	
	Jon Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,3,8-11,17 and 24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,3,8-11,17 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 March 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Action is in response to the communication filed on 5/5/2006.

The amendment filed 5/5/2006 is acknowledged and has been entered.

Claims 2, 3, 8-11, 17, and 24 are currently pending in the application and are addressed herein.

Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Claim Rejections - 35 USC § 102

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. Claims 2, 3 and 17 are rejected under 35 U.S.C. 102(b) based upon a public use or sale of the invention.

It is noted that claim 2 is drawn to "An isolated nucleic acid encoding a protein... wherein said protein [is encoded by SEQ ID NO: 1 or SEQ ID NO: 4]... **or a nucleotide sequence complementary to one of SEQ ID NO: 1 or SEQ ID NO: 4**..." Given the broadest reasonable interpretation consistent with the specification, the phrase "or a nucleotide sequence complementary to one of SEQ ID NO: 1 or SEQ ID NO: 4" encompasses any nucleotide

sequence that is complementary to SEQ ID NO: 1 or SEQ ID NO: 4. That is, the "nucleotide sequence complementary to one of SEQ ID NO: 1 or SEQ ID NO: 4" is not specifically limited to a sequence that encodes a protein functionally identical to a protein encoded by SEQ ID NO: 1 or SEQ ID NO: 4. Therefore, the claims encompass any nucleic acid sequence that is complementary to any part of SEQ ID NO: 1 or SEQ ID NO: 4.

As such, an oligonucleotide that is 6 nucleotides long (i.e., a hexanucleotide) and which is 100% identical to 6 nucleotides of SEQ ID NO: 1 or SEQ ID NO: 4 would be encompassed by the claims as it would be a nucleotide sequence complementary to one of SEQ ID NO: 1 or SEQ ID NO: 4. Claim 3 is drawn to the isolated nucleic acid of claim 2 wherein the nucleic acid is obtained from a natural, synthetic or half-synthetic source. Claim 17 encompasses a reagent that is at least one nucleic acid according to claim 2.

Random hexanucleotides (i.e., 6mers) were available for sale as early as 1997 (see 1997 Boehringer Mannheim Catalog, page 95, previously cited). The hexanucleotide mix available comprised, "mixture of hexamer nucleotides of all possible sequences for random primed DNA labeling." Therefore, there existed within the hexanucleotide mix at least one nucleotide sequence that would be 100% identical part of SEQ ID NO: 1 and SEQ ID NO: 4. Claim 3 encompasses the nucleotide sequence of claim 2 that is obtained from natural, synthetic or half-synthetic source. The hexamers for sale by Boehringer were synthetically synthesized.

It is noted that amending the claims to be limited in scope to the nucleotide sequences that are SEQ ID NO: 1 and SEQ ID NO: 4 would obviate this rejection.

3. Claims 2, 3 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Mierendorf et al. (U.S. patent 5,629,179).

It is noted that claim 2 is drawn to "An isolated nucleic acid encoding a protein... wherein said protein [is encoded by SEQ ID NO: 1 or SEQ ID NO: 4]... **or a nucleotide sequence complementary to one of SEQ ID NO: 1 or SEQ ID NO: 4**..." Given the broadest reasonable interpretation consistent with the specification, the phrase "or a nucleotide sequence complementary to one of SEQ ID NO: 1 or SEQ ID NO: 4" encompasses any nucleotide sequence that is complementary to SEQ ID NO: 1 or SEQ ID NO: 4. That is, the "nucleotide sequence complementary to one of SEQ ID NO: 1 or SEQ ID NO: 4" is not specifically limited to a sequence that encodes a protein functionally identical to a protein encoded by SEQ ID NO: 1 or SEQ ID NO: 4. Therefore, the claims encompass any nucleic acid sequence that is complementary to any part of SEQ ID NO: 1 or SEQ ID NO: 4.

Mierendorf et al. teaches a method and kit for making a cDNA library wherein the kit comprises random octamer oligonucleotides (i.e. nucleic acids that are 8 nucleotides in length) over every possible sequence (see column 7, line 59-column 8, line 6). Mierendorf et al. teaches a kit comprising every possible octamer oligonucleotide. Therefore, the kit taught by Mierendorf et al. includes 8mer (i.e. octamer) oligonucleotides which are complementary to part of SEQ ID No. 1 and SEQ ID No. 4.

It is noted that amending the claims to be limited in scope to the nucleotide sequences that are SEQ ID NO: 1 and SEQ ID NO: 4 would obviate this rejection.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2, 3, 8-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 recites the phrase, "wherein said protein has a nucleotide sequence indicated in either SEQ ID NO: 1..." in line 5.

This phrase renders the claim indefinite because proteins are comprised of amino acid sequences, not nucleotide sequences. Therefore it is unclear how the protein can have a nucleotide sequence.

It is noted that amending the indicated phrase to " wherein said protein is encoded by the nucleotide sequence of SEQ ID NO: 1 or SEQ ID NO: 4" would obviate this rejection.

It is noted that claims 3, 8-11 are rejected because they are dependent claims that encompass all of the embodiments of claim 2.

Claim 11 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 11 recites the limitation "The transformed host cell" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claims 17 and 24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claims 17 and 24 the phrase "in particular" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claim Rejections - 35 USC § 112, first paragraph (scope of enablement)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 10 and 11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for "an isolated transformed host cell", does not reasonably provide enablement for a non-isolated transformed host cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Claims 10 and 11 are drawn to "a transformed host cell" and "the transformed host cell" comprising an isolated nucleic acid molecule. It is noted that the claims are not limited to "an isolated host cell". As such, and in view of the disclosure that the host cell can be "a constituent of a living organism, e.g., a transgenic mouse" (e.g., see page 4, last paragraph). Therefore, the

instant claims encompass a transformed host cell wherein the host cell is a non-isolated cell, such as a transformed cell in a transgenic animal.

The claims encompass "a host cell" comprising a nucleic acid sequence, wherein the cells can be non-isolated cells (i.e., cells within a transgenic animal). As indicated above, the specification also contemplates transgenic animals that have been genetically engineered such that the transgenic animals comprise the claimed nucleic acids or cells. Therefore, given the broadest reasonable interpretation, the claims encompass transgenic animals which have been genetically engineered to comprise the claimed sequences and cells.

With respect to making transgenic animals, it is noted that the prior art recognizes that making such genetically modified animals is unpredictable. For instance, the relevant art has for many years stated that the unpredictability of making transgenic animals lies with the site or sites of integration of the transgene into the target genome. Transgenic animals are regarded to have within their cells mechanisms which prevent expression of the transgene, such as DNA methylation or deletion from the genome (**Kappel et al.** (1992) Current Opinion in Biotechnology, Vol. 3, p. 549, col. 2, parag. 2). Furthermore, **Mullins et al.** states that not all animals express a transgene sufficiently expresses the transgene as the integration of a transgene into difference species of animal has been reported to given divergent phenotypes (**Mullins et al.** (1993) Hypertension Vol. 22, page 631, col. 1, parag. 1, lines 14-17). Also, **Mullins et al.** (1996) teaches that "the use of nonmurine species for transgenesis will continue to reflect the suitability of a particular species for the specific questions being addressed, bearing in mind that a given construct may react very differently from one species to another." (**Mullins et al.** (1996) J. Clin. Invest. Vol. 97, page 1559, Summary). Furthermore, well-regulated expression of the

transgene is not frequently achieved because of poor levels or the complete absence of expression or leaky expression in non-target tissues (**Cameron** (1997) Molec. Biol. Vol. 7, page 256, col. 1 -2, bridg. parag.). Factors influencing low expression, or the lack thereof, are not affected by copy number and such effects are seen in lines of transgenic mice made with the same construct (**Cameron** (1997), page 256, lines 3-9). These factors, thus, are copy number independent and integration site dependent, emphasizing the role the integration site plays on expression of the transgene (**Cameron** (1997), page 256, lines 10-13).

While, the intent is not to say that genetically modified animals can never be made, the intent is to provide art taught reasoning as to why the instant claims are not enabled to their full scope. Given such species differences in the expression of a transgene, particularly when taken with the lack of guidance in the specification, it would have required undue experimentation to predict the results achieved in any engineered mammal comprising the claimed cell(s).

Considering the nature of the invention, the breadth of the claims, the unpredictable nature of the invention as recognized in the prior art, the limited amount of working examples and guidance provided, and the high degree of skill required to practice the invention, it is concluded that the specification does not provide an enabling disclosure for the full scope of the instant claims. Therefore, additional experimentation is required before one of skill in the art could make and use the claimed invention to the full scope encompassed by the claims. The amount of additional experimentation required to perform the broadly claimed invention is undue.

Claim Rejections - 35 USC § 112, first paragraph (written description)

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 24 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 24 encompasses a nucleic acid that is a splice variant which hybridizes with the nucleotide sequence indicated in SEQ ID NO: 1 or SEQ ID NO: 4. Therefore, given the broadest reasonable interpretation of the claims, the claims encompass a genus of splice variant nucleic acid molecules which potentially includes thousands of different nucleic acids sequences.

The written description guidelines note regarding such genus/species situations that "Satisfactory disclosure of a 'representative number' depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for written description.) Here, the specification has not described any splice variants, nor does the prior art appear to teach any splice variants of SEQ ID NO: 1 or SEQ ID NO: 4.

With regard to the written description, the claim encompasses splice variant sequences which are different from those disclosed as SEQ ID NO: 1 and SEQ ID NO: 4 for which no written description is provided in the specification.

It is noted that in Fiers v. Sugano (25 USPQ2d, 1601), the Fed. Cir. concluded that

> "...if inventor is unable to envision detailed chemical structure of DNA sequence coding for specific protein, as well as method of obtaining it, then conception is not achieved until reduction to practice has occurred, that is, until after gene has been isolated...conception of any chemical substance, requires definition of that substance other than by its functional utility."

In the instant application, only the sequences of the disclosed SEQ ID NO: 1 and SEQ ID NO: 4. are described.

Also, in Vas-Cath Inc. v. Mahurkar (19 USPQ2d 1111, CAFC 1991), it was concluded that:

> "...applicant must also convey, with reasonable clarity to those skilled in art, that applicant, as of filing date sought, was in possession of invention, with invention being, for purposes of "written description" inquiry, whatever is presently claimed."

In the application at the time of filing, there is no record or description which would demonstrate conception or written description of any splice variants of SEQ ID NO:1 or SEQ ID NO:4.

Claim Objections

Claim 2 is objected to because the amendment filed 5/5/2006 has deleted the period from the end of the claim. MPEP 60801(m) states,

> "Each claim begins with a capital letter and ends with a period. Periods may not be used elsewhere in the claims except for abbreviations. See Fressola v. Manbeck, 36 USPQ2d 1211 (D.D.C. 1995). All claims must be a single sentence that end with a period."

Appropriate correction is required.

Applicant is advised that should claim 10 be found allowable, claim 11 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing,

despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). In the instant case, the only difference between claim 10 and 11 is that claim 10 is drawn to "A recombinant DNA vector...", while claim 11 is drawn to "The recombinant DNA vector..."

Claim 8 is objected to because the phrase, "said DNA vector molecule expressing protein pKe#122..." is awkward. Applicants are asked to consider amending the indicated phrase to "where said DNA vector expresses protein pKe#122..." which more clearly describes the claimed subject matter.

Response to Arguments

Applicant's arguments filed 5/5/2006 have been fully considered.

The cancellation of claims 4-7 and 18-20 render all rejections/objections of these claims moot.

With respect to the rejection of claims 2, 3, 17 under 325 USC 102(b) based upon a public use or sale of the invention, Applicants argue that the claims have been amended to overcome this rejection. Specifically, Applicants argue that claim 2 is directed to oligonucleotides that hybridize to SEQ ID NO:1 and SEQ ID NO:4 under specific hybridization conditions. Applicants argue that the hexanucleotides taught by Boehringer Manheim Catalog are, therefore, not encompassed by the claims (e.g., see 7 of the 5/5/2006 communication).

In response, it is respectfully pointed out that claim 2 does not comprise any specific hybridization conditions (the hybridization conditions have been deleted from the claim).

Furthermore, the hexanucleotide sequences of Boehringer Mannheim Catalog would include hexanucleotides which are 100% identical to each six-nucleotide sequence of SEQ ID NO: 1 and SEQ ID NO: 4, which would certainly hybridize to SEQ ID NO: 1 and 4 under stringent conditions. Therefore, Applicants arguments are not persuasive.

With respect to the rejection of claims 2, 3, 17 under 35 USC 102(b) as being anticipated by Mierendorf, Applicants argue that Mierendorf does not teach each and every element of the claims. It is noted that Applicants acknowledge that Mierendorf teaches the generation of random primers. Applicants argue that Mierendorf does not teach or disclose which random primers will hybridize to SEQ ID NO: 1 or SEQ ID NO: 4 or which conditions would be necessary to achieve hybridization. Applicants argue that undue experimentation would be required and that Mierendorf does teach appear to teach each and every limitation of the claims.

In response, it is respectfully pointed out that Mierendorf teaches the production of a composition comprising every possible octamer nucleotide sequence. Therefore, Mierendorf teaches a composition comprising octamer sequences that are 100% identical to every possible 8 nucleotide sequence of SEQ ID NO: 1 and SEQ ID NO: 4. One of skill in the art would clearly recognize that the sequences that are 100% identical to 8 nucleotide sequences of SEQ ID NO 1 and SEQ ID NO: 4 would hybridize to SEQ ID NO: 1 and SEQ ID NO: 4 under even stringent hybridization conditions (not that the claims require hybridization under any particular conditions). Furthermore, it is irrelevant if Mierendorf points to specific octamers which would hybridize to SEQ ID NO: 1 and SEQ ID NO: 4, the fact the Mierendorf teaches a composition comprising every possible octamer is sufficient to show a teaching of "an isolated nucleic

nucleotide sequence complementary to one of SEQ ID NO: 1 or SEQID NO: 4" which are the structural limitations of the claims that must be met in order to anticipate the instant claims. Therefore, Applicants arguments are not persuasive.

With respect to the rejection of claims under 35 USC 112, 1st paragraph (new matter) the amendment to the claims obviates this rejection.

With respect to the rejection(s) of claim(s) under 35 USC 112, 1st paragraph (written description), Applicants arguments have been fully considered and (in view of the amendment) are persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of the amendment to claim 24 which adds the limitation that the nucleic acid is a splice variant.

With respect to the objection to claims 3, 4, 5 and 18, the cancellation of claims 4, 5 and 18 renders the objection moot.

It is also noted that upon further consideration, a new ground(s) of rejection is made under 35 USC 112, second paragraph, 35 USC 112, first paragraph for the reasons indicated herein.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon Eric Angell whose telephone number is 571-272-0756. The examiner can normally be reached on Mon-Fri, with every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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